REMARKS

Claims 1-19 and 24-63 were pending in the subject application. Claims 1, 5-13, 18-19, and 24-37 were under examination. By this Amendment, claim 18 has been canceled. Accordingly, the claims now under examination are claims 1, 5-13, 19 and 24-37. Pending claims 2-4, 14-17, and 38-63 have been withdrawn from consideration as being drawn to nonelected inventions.

The subject application has been found to be patentable over the prior art of record. Applicants acknowledge withdrawal of two of the previous grounds of rejection under Section 112, second paragraph. (December 30, 2002 Office Action, page 3).

CONSIDERATION OF INFORMATION DISCLOSURE STATEMENT

The Office Action stated, "The references cited on the various Information Disclosure Statements (Papers Nos. 5-8) that were not previously considered remain unavailable. As, stated previously, said references will be considered when they become available." An Information Disclosure Statement, including copies of the documents cited therein, is being filed concurrently herewith.

REFERENCE TO PRIOR APPLICATION

The Office Action incorrectly stated the following:

> Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. . . . Applicant states in their [October 15, 2002] response that on March 14, 2002 they 'amended the reference to the prior application to insert the Provisional Application number assigned to the prior application. Said paper (Paper

> No. 15) is a request to correct the filing receipt for the instant application and does not contain an amendment to the specification.

(December 30, 2002 Office Action, pages 2-3). On March 14, 2002 applicants submitted by facsimile a Preliminary Amendment that amended the specification to refer to the prior applications whose benefit is claimed by applicants. A copy of the March 14, 2002 Preliminary Amendment is enclosed, including a copy of the Facsimile Receipt indicating that all four pages of the Preliminary Amendment were received by the Office on March 14, 2002 (Exhibit A). Inspection of the enclosed copy of the March 14, 2002 submission will reveal that it is a Preliminary Amendment and not a request for corrected filing receipt. Accordingly, applicants respectfully maintain that they have complied with the requirements of 37 CFR 1.78(a)(2) and (a)(5). The March 14, 2002 Preliminary Amendment is entitled to entry.

Applicants did submit Communications Requesting Corrected Filing Receipt on March 21 and again on April 5, 2002. Those submissions were separate from and should not be confused with the March 14, 2002 Preliminary Amendment. A corrected filing receipt was issued by the Office on July 5, 2002.

CLAIMS ARE ENABLED

Claims 1, 5-13, 18-19 and 24-37 have been rejected under 35 U.S.C. 112, first paragraph, on the grounds that "the specification, while being enabling for methods utilizing **VSV** for reducing the viability of mylogenous [sic] leukemia cell lines *in vitro*, does not provide enablement for the utilization of **VSV** for the reduction of viability of all hematopoietic tumor cells (either *in vivo* or *in vitro*)." (December 30, 2002 Office Action, page 4) (emphasis in original). This rejection is respectfully traversed.

First, the Office has improperly sought to place on applicants the burden of proving that the invention works. This is illustrated by the following passage from the rejection with respect to the tumor cells recited in the claims:

> "Additionally, the instant claims are drawn to **all** forms of hematopoietic tumor cells, while the specification has demonstrated only two leukemia cell lines (MD7E and L1210), a couple of AML cell lines OCI/AML3 and AML5, one CML cell line (K-562) and a T-cell leukemia (MOLT-4) that are that are susceptible to VSV infection."

(June 12, 2002 Office Action, page 4) (bolding in original, underlining added). In addition to the six cell types acknowledged by the rejection, the application also contains experimental results demonstrating that two myeloma cell types (SR and H929) are also susceptible to VSV infection. (Specification, Example 19, Table 8 on page 45).

Contrary to the clear implication of the rejection, applicants are not required to submit experimental results demonstrating the anti-tumor activity of vesicular stomatitis virus. Rather, the Office bears the burden of establishing that the specification does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. As stated by the CCPA in In re Marzocchi:

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, ___ (underlining added). It is not sufficient for the Office to simply assert that it doubts the correctness of the statements in the disclosure. The Office must back up its doubts with evidence or reasoning. Again from In re Marzocchi:

> "In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."

In re Marzocchi, 439 F.2d at 224, 169 USPQ at ___ (internal citations omitted) (underlining added). No evidence or reasoning has been cited in support of the rejection. The mere insertion of the word "only" before a list of what applicants have shown experimentally does not qualify as acceptable evidence or reasoning to sustain an enablement rejection. To the contrary, the demonstrated success in a variety of hematopoietic tumor cells further supports applicants' position that the invention works for its intended purpose.

Second, although the June 12, 2002 Office Action focused on the supposed failure of the application to demonstrate that a wider variety of hematopoietic tumor cells are susceptible to VSV infection as seen from the above-quoted passage from page 4 of the June 12, 2002 Office Action, the December 30, 2002 Office Action now casts the rejection as one of alleged failure to name a sufficient number of hematopoietic tumor cells. Thus the rejection states:

> As outlined in the previous Office action, the instant claims are drawn to using VSV to all forms of hematopoietic tumor cells, while the specification is silent on what hematopoietic tumor cells (other than a few cell lines) are susceptible to the anti-tumor effect of VSV. . .

(December 30, 2002 Office Action, page 5) (emphasis in original). As seen from the above-quoted passage from the Office Action the rejection criticizes the application for not naming all of the different types of hematopoietic tumor cells. This ground of rejection is not well taken since it is well-established that "a patent need not teach, and

preferably omits, what is well known in the art." (Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, ___ (Fed. Cir. 1986), *citing* Lindemann Maschinenfabrik v. American Hoist and Derrick, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The specification teaches that "VSV has a broad host range and is capable of infecting most types of human cells, whereas other viruses are more limited in regard to the types of cells they may effect". (Specification, page 6, lines 27-29). In view of the broad host range of VSV, the person of ordinary skill in the art would not require undue experimentation to practice the invention.

Third, the Office has also improperly tried to place on applicants the burden of proving that the invention works *in vivo*. The rejection stated:

> "Claims 32-34 are drawn to the *in vivo* application of the claimed methods. People of skill in the art require documented evidence that a benefit can be derived by the therapeutic application of a given substance; however a survey of the relevant art does not indicate that substances such as those claimed provide such benefit."

(June 12, 2002 Office Action, page 4). (To avoid possible confusion arising from the above-quoted passage in the Office Action applicants note that all of the claims encompass *in vivo* administration, not just claims 32-34.) Based on the above-quoted passage from the rejection, one might think that the application contains no *in vivo* results, but it does. The specification contains *in vivo* data demonstrating the efficacy of VSV in treating human melanoma xenografts in nude mice. (Example 25, page 49).

Moreover, the rejection has tried to shift the enablement burden to applicants by putting the Office's unsupported doubts in the mouth of unnamed, hypothetical "people of skill in the art" who are said to "require documented evidence that a benefit can be derived by the therapeutic application [i.e. *in vivo*] of a given substance." The unsupported citation

to hypothetical "people of skill in the art" obscures such crucial issues as which people require such evidence, whether they are a minority or a majority of those of skill in the art, what evidence would they consider adequate, and the purpose for which they require such evidence. The purpose for which they allegedly require the evidence is necessary to avoid improperly importing into the enablement context the more stringent requirements under the Food and Drug Act for approval to market a therapeutic agent. It is, of course, important not to confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, _____ (Fed. Cir. 1995), citing, Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

The Office has attempted to require applicants to prove that the *in vitro* data contained in the specification correlate to an *in vivo* benefit. The rejection stated:

> "[T]he specification . . . does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said viruses are administered *in vivo* to 'treat' hematopoietic tumor cells, although *in vivo* use is clearly encompassed by the claims. Lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating *in vitro* data as exemplified with *in vivo* benefit, the specification cannot be said to teach how to use the claimed viruses as pharmaceuticals."

Office Action, paragraph bridging pages 4-5. Applicants respectfully submit that it is accepted in the art to which this invention pertains that *in vitro* evidence of antitumor effect on tumor cell lines is reasonably correlated to *in vivo* therapeutic efficacy. The correlation is illustrated by the Pecora, et al. article submitted previously. It is also illustrated by U.S. Patent No. 5,677,178 (McCormick). The only experimental results contained in McCormick are the results of *in vitro* testing (Patent No. 5,677,178, column 18, line 42 to column 20, line 23; and Figures 2A-3C). Neverthless McCormick bases his

teaching of human therapy on those *in vitro* results (Patent No. 5,677,178, column 16, line 45 to column 18, line 25).

In maintaining the rejection the Office has cited several articles, which together demonstrate nothing more than the unsurprising observation that the *in vitro* environment cannot duplicate the *in vivo* environment exactly. Nevertheless, it is undeniable that *in vitro* experiments continue to be performed and relied upon to identify treatments for *in vivo* use. If the rejection was correct that "clinical correlations are generally lacking", *in vitro* experiments would not be as widely used as they are.

Moreover as mentioned above, the specification does contain *in vivo* data demonstrating the efficacy of VSV in treating human melanoma xenografts in nude mice. (Example 25, page 49). These results support applicants' position that the *in vitro* activity of VSV is correlated with *in vivo* efficacy.

Fourth, initially the Office improperly sought to place on applicants a separate burden of explaining the mechanism by which the claimed invention works. This rejection stated, "The specification is silent on what receptor is utilized by VSV for cell entry." (June 12, 2002 Office Action, page 4). As seen from the above-quoted passage, the Office has taken the position that the specification is required to explain how the viruses of the claimed invention enter the cells that they infect. That position is contrary to law because, "it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 U.S.C. §112." Cross v. Iizuka, 753 F.2d 1040, 1042, 224 USPQ 739, ____ (Fed. Cir. 1985), citing Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983). The Office now acknowledges that there is no requirement to disclose the receptor. Instead it now states that "the Specifications [sic] silence with regard to what receptor was utilized by VSV was merely an illustration of the total lack of guidance provided by the specification with regard to

what types of hematopoietic tumor cells could be treated by the methodologies of the instant invention". (December 30, 2002 Office Action, pages 7-8). The guidance provided by the specification as to the tumor cells that can be treated in accordance with this invention is discussed above.

Fifth, the Office has improperly sought to build an enablement rejection out of qualified statements in the specification concerning mechanism. The rejection stated, "The invention is predicated on the susceptible tumor cells lacking PKR activity, but the specification is silent on which hematopoietic tumor cells lack said function." (June 12, 2002 Office Action, page 4). Contrary to the above-quoted assertion from the rejection, applicants' invention is not limited to tumor cells that lack PKR activity. No such limitation appears in claim 1. The statement in the specification that "[p]referably the tumour cell lacks PKR activity" (Specification, page 4, lines 8-9) (underlining added) and the recitation of tumor cells lacking substantial PKR activity in dependent claims 18 and 19 are further evidence that the invention as a whole is not "predicated on the susceptible tumor cells lacking PKR activity". Understanding the instant invention as being "predicated on the susceptible tumor cells lacking PKR activity" is all the more unreasonable in view of applicants' express warning that their discussion of PKR's possible role was being advanced "[w]ithout being bound by theory" (Specification, page 14, lines 14-18, esp. line 14).

The Office has responded that "the specification only provides guidance for the selective in vitro killing of a few PKR- cell lines." (December 12, 2002 Office Action, page 8). That is wrong. The rejection once again confuses guidance with examples proving efficacy. The specification does provide guidance for practicing the full scope of the invention. The Office is once again attempting to improperly impose on applicants the burden of proving effectiveness, contrary to the law as discussed above.

Sixth, the Office has faulted the specification for being silent where it allegedly should not have been. The rejection stated:

> "[T]he specification is . . . silent on which interferon other than alpha interferon would provide normal cells protection from viral infection. . . . [T]he specification is . . . silent on how said viruses are to be administered to said subject."

(June 12, 2002 Office Action, page 4). The reference to interferon presumably applies only to claims 24 and 37, which recite interferon. In accordance with this invention any interferon can be utilized. The invention as claimed does not rest on the selection of certain types of interferon. The Office has now responded that "the specification is silent on the optional use of any interferon other than alpha interferon." (December 12, 2002 Office Action, page 8). As seen from the above-quoted passage from the Office Action the rejection criticizes the application for not naming all of the different types of interferon. This ground of rejection is not well taken since it is well-established that "a patent need not teach, and preferably omits, what is well known in the art." (Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, ___ (Fed. Cir. 1986), *citing* Lindemann Maschinenfabrik v. American Hoist and Derrick, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

With respect to how the virus is administered to a subject, all conventional techniques and routes of *in vivo* administration can be utilized. The invention as claimed does not rest on the selection of certain types of interferon or (other than claim 32) certain routes of administration from among those known in the art.

In maintaining this ground of rejection the Office has cited one passage in the specification and a Scientific American article, both of which are apparently cited for the proposition that the intravenous route allegedly would not work. With regard to the specification the rejection stated:

> Applicant argues that all methodologies known in the art would be effective. This however contradicts Applicant's assertion in the Specification. Applicant states on page 33 of the Specification that PKR -/- mice were killed with VSV by several routes of infection but that these mice were not affected by intravenous injections of the virus.

(December 30, 2002 Office Action, page 5). The passage referred to in the above-quoted passage from the rejection refers to an assay to screen mice, not tumors. No tumor was involved in the PKR-/- mice. Therefore this statement in the specification does not support the rejection's position that intravenous injection of VSV would not be effective against tumors.

Next, the rejection cites Jain, Scientific American (July 1994) for the proposition that there are various impediments to delivery of drugs into solid tumors (December 30, 2002 Office action, pages 5-6). While the issues cited in the Jain article may be theoretically interesting, it is important to bear in mind that many anti-cancer drugs have been demonstrated to be effective against solid tumors even when administered intravenously.

Moreover, the specification does contain *in vivo* data demonstrating the efficacy of intravenous VSV in treating human melanoma xenografts in nude mice. (Example 25, page 49). Thus in contrast to the rejection's reliance on theoretical concerns that may or may not be valid in any particular case, the specification contains actual experimental results demonstrating the anti-tumor efficacy of VSV administered intravenously.

In view of the foregoing, applicants respectfully submit that the enablement rejection is improper and should be withdrawn.

CLAIMS NOT INDEFINITE

Claims 1, 5-13, 18-19, and 24-37 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is respectfully traversed. The rejection sets forth three grounds of rejection, each of which is addressed by applicants in turn as follows:

1) The rejection stated that claim 1 is rendered vague and indefinite by the use of the term "administering to the tumor cell a virus". The rejection stated that it "is unclear what is meant by said term. Is said virus 'injected' into said tumor cell or merely introduced into said cells [sic] environment?" (July 12, 2002 Office Action, page 5). In accordance with this invention, the virus can be administered to the tumor cell utilizing any conventional technique. Of course, "breadth is not to be equated with indefiniteness." In re Miller, 441 F.2d 689, 693, 169 USPQ 597, ____ (CCPA 1971).

In maintaining the rejection the Office stated:

> Applicant's arguments have been fully considered and deemed non-persuasive. It is still unclear what is meant by said phrase. What are considered to be conventional methods of "administering"? As written, it is still impossible to determine the metes and bounds of the claimed invention.

(December 30, 2002 Office Action, page 9). In response, applicants respectfully submit that the person of ordinary skill in the art who is doing something to cells with a vesicular stomatitis virus would have no difficulty in determining whether what he is doing is "administering" the virus or not. Accordingly, those skilled in the art will be in no uncertainty concerning what subject matter falls within the scope of the claims. (In re Miller, 441 F.2d 689, 693, 169 USPQ 597, ____ (CCPA 1971)). Section 112, second paragraph, requires nothing more.

2) The rejection stated that claim 18 is rendered vague and indefinite by the use of the term "substantially no PKR activity". Without conceding the correctness of this rejection and in an effort to advance prosecution, applicants have cancelled claim 18.

3) The rejection stated that claim 24 is rendered vague and indefinite by the use of the term "administering interferon to the tumor cell". The rejection stated that it "is unclear what is meant by said term. Is said virus [sic, interferon?] 'injected' into said tumor cell or merely introduced into said cells [sic] environment?" (July 12, 2002 Office Action, page 6). In accordance with this invention, interferon can be administered to the tumor cell utilizing any conventional technique. Again, "breadth is not to be equated with indefiniteness." In re Miller, 441 F.2d 689, 693, 169 USPQ 597, ____ (CCPA 1971).

In maintaining the rejection the Office stated:

> Applicant's arguments have been fully considered and deemed non-persuasive. It is still unclear what is meant by said phrase. What are considered to be conventional methods of "administering"? As written, it is still impossible to determine the metes and bounds of the claimed invention.

(December 30, 2002 Office Action, page 10). In response, applicants respectfully submit that the person of ordinary skill in the art who is doing something to cells with interferon would have no difficulty in determining whether what he is doing is "administering" or not. Accordingly, those skilled in the art will be in no uncertainty concerning what subject matter falls within the scope of the claims. (In re Miller, 441 F.2d 689, 693, 169 USPQ 597, ____ (CCPA 1971)). Section 112, second paragraph, requires nothing more.

CONCLUSION

Reconsideration and withdrawal of all rejections and objections is respectfully requested.

If any fee is required in connection with the filing of this Amendment, the Commissioner is hereby authorized to charge the amount of such fee to Deposit Account No. 50-1677.

Respectfully submitted,

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